## REMARKS

### *Status of the Claims*

Claims 1-6, 10, 13-20, 24, 27-32, 36, 39-41, 45 and 48-57 were in the application.

Claims 14-20, 24, 27-32, 36, 40, 41, 45 and 53-57 have been withdrawn from consideration as directed to a non-elected invention.

Claims 1-6, 10, 13, 39 and 48-52 were rejected.

Claims 1, 2 and 39 have been amended. Claims 6, 14-20, 24, 27-32, 36, 40, 41, 45, 51 and 53-57 have been canceled without prejudice.

Upon entry of this amendment, claims 1-5, 10, 13, 39 and 48-50, and 52 will be pending.

### *Summary of the Amendment*

Claims 1 and 2 have been amended to correct typographical errors. Claim 39 has been rewritten in independent form. Claims 6 and 51 have been canceled without prejudice. Claims 14-20, 24, 27-32, 36, 40, 41, 45 and 53-57 have been canceled as directed to non-elected subject matter..Support for these amendments can be found throughout the specification. No new matter has been added.

### *Allowable Subject Matter*

Applicants note that on the "Office Action Summary" page, claim 39 is included as a rejected claim but was not included in any of the rejections or objections. Claim 39 has been rewritten as an independent claim and is allowable in its current form. In view of the foregoing, Applications respectfully request that claim 39 be deemed allowable.

### *Priority*

The Office alleges that the claim to benefit of a prior filed application under 35 U.S.C. § 119(e) is not proper because the prior filed application (U.S. Provisional Application No. 60/513,489), allegedly fails to provide adequate support or enablement as required under 35 U.S.C. § 112, first paragraph. The Office alleges that the provisional application does not

provide support for the claimed method steps recited because the Office alleges that the provisional application "is vastly devoted to the relationship between eIF2C2 and let-7, not the claim the claimed siRNA identification methods." (Office Action, page 4). Applicants respectfully disagree.

The present application's priority claim to U.S. Provisional Application No. 60/513,489 ('489 application) under 35 U.S.C. § 119(e) is proper because the '489 application adequately describes the method and enables the method. Claim 1 recites:

> A method of identifying a uniquely targeting siRNA nucleotide sequence for a target mRNA sequence of a target species comprising the steps of:
>
> comparing a database of mRNA sequences from the target species with an siRNA nucleotide sequence that consists of 18-25 including at least 11 consecutive nucleotides complementary to the target mRNA sequence to be cleaved by the siRNA nucleotides, wherein the at least 11 consecutive nucleotides complementary to the target mRNA sequence include a nucleotide that is third from an siRNA nucleotide sequence's 5' end; and
>
> determining if, in addition to the target mRNA sequence, one or more additional mRNA sequences in the database are complementary to an 11 consecutive nucleotide sequence of the siRNA nucleotide sequence including the third nucleotide from the 5' end of the siRNA nucleotide,
>
> wherein an absence of one or more additional mRNA sequences in the database that are complementary to an 11 consecutive nucleotide sequence of the siRNA nucleotide sequence including the third nucleotide from the 5' end of the siRNA nucleotide indicates that the siRNA nucleotide sequence is a uniquely targeting siRNA nucleotide sequence

The '489 provides adequate written description support such that one of skill in the art reading the '489 application could immediately envisage the claimed invention. The '489 application supports a method of identifying a uniquely targeting siRNA. For example, the '489 application teaches one of skill in the art how to design siRNAs with high specificity. The '489 application states, "In order to design siRNAs with high specificity, and to avoid off-target

effects, these nucleotides should not share homology with any mRNA but the one that is targeted." ('489 application, p. 7, last sentence). One of skill in the art would understand that the '489 application discloses a method of how to identify (design) a siRNA.

The specification also provides adequate support for the step of:

> comparing a database of mRNA sequences from the target species with an siRNA nucleotide sequence that consists of 18-25 including at least 11 consecutive nucleotides complementary to the target mRNA sequence to be cleaved by the siRNA nucleotides, wherein the at least 11 consecutive nucleotides complementary to the target mRNA sequence include a nucleotide that is third from an siRNA nucleotide sequence's 5' end; and

The specification states that the siRNA should not "share homology with any mRNA but the one that is targeted." One of skill in the art would understand that this would involve comparing the propose targeted sequence with a database of mRNA sequences. The specification discloses the use of the 11 nucleotides including the third from an siRNA nucleotide sequence's 5' end. For example, the specification states at page 7, "that the critical determinant of siRNA specificity ... are the nucleotides shown in Figure 4." Figure 4 shows a sequence that is complementary to 11 nucleotides, starting at the third nucleotide of the siRNA molecule. The specification describes Figure 4 as describing the "Minimal requirements for target RNA recognition and cleavage by mi/siRNAs." The figure shows the 11 "nucleotides ... that are critical for target recognition and cleavage are shown base-paired with the target RNA nucleotides." ('489 specification, p.14).

The specification also adequately describes and enables:

> determining if, in addition to the target mRNA sequence, one or more additional mRNA sequences in the database are complementary to an 11 consecutive nucleotide sequence of the siRNA nucleotide sequence including the third nucleotide from the 5' end of the siRNA nucleotide,
>
> wherein an absence of one or more additional mRNA sequences in the database that are complementary to an 11 consecutive nucleotide sequence of the siRNA nucleotide sequence including the third nucleotide from the 5' end of the

siRNA nucleotide indicates that the siRNA nucleotide sequence is a uniquely targeting siRNA nucleotide sequence. (Claim 1)

The specification states that "siRNAs with high specificity ... should not base-pair with any mRNA but the one to be targeted." ('489 specification, p.14). One of skill in the art would understand that to confirm whether or not the siRNA would not base-pair with any mRNA but the one to be targeted would require determining if other than the target mRNA there are additional mRNAs in a database that are complementary. Although the exact language of the claims is not used in the '489 application the method is clearly disclosed. The '489 application discloses the requirements of identifying a unique siRNA and all that the present application provides is other embodiments of what was already described in the '489 application.

The Office has failed to present any evidence as to why the '489 application has not enabled the presently claimed invention. Nothing more than routine experimentation would be required to practice the methods disclosed in the '489 application. Using databases to compare sequences is routine in the art. The present application provides the parameters to be used in the comparison. One of skill in the art reading the '489 application would understand that the parameters includes comparing at least 11 nucleotides including the third nucleotide from the 5' end of the siRNA nucleotide sequence.

Accordingly, the present application is entitled to priority under 35 U.S.C. § 119(e) and the effective filing date of the present application should be at least the filing date of the '489 application, which is October 22, 2003. In view of the foregoing, Applicants respectfully request that the Office declare that the priority claim is proper.

***Claim Objections***

Claim 1 was objected for an alleged informality. The Office alleges that the word "nucleotides" is necessary immediately following "18-25 in line 4 of claim 1. Applicants have inserted the term "nucleotides" obviating this objection.

Claim 6 was objected to under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of the claim from which it depends.

The Office alleges that claim 6 does not further limit claim 1. Claim 6 has been canceled rendering this objection moot.

Claim 51 was objected to under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of the claim from which it depends. The Office alleges that claim 51 does not further limit claim 2. Claim 51 has been canceled rendering this objection moot.

***Claim Rejections Under 35 U.S.C. § 112, second paragraph***

Claims 1-5 and 48-50 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Office alleges that claims 1 and 2 recitation of "the siRNA nucleotides" and "the siRNA nucleotide," and claims 3-5 and 48-50 recitation of "the database of mRNA sequences" do not have sufficient antecedent basis for these phrases.

Applicants have amended claims 1 and 2 to correct an inadvertent grammatical error. Claims 1 and 2 have been amended to recite "the siRNA nucleotide sequence." Accordingly, claims 1 and 2 are definite.

Applicants respectfully disagrees that there is insufficient antecedent basis for the phrase "the database of mRNA sequences." Claims 1 and 2 both recite, in part, "comparing a database of mRNA sequences." Claims 3-5 and 48-50 refer to the same database of mRNA sequences. Accordingly, there is proper antecedent basis for the phrase. Therefore, claims 3-5 and 48-50 are definite.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

***Claim Rejections Under 35 U.S.C. § 102***

Claims 1-6, 10, 13, 48-52 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Liu *et al.* (U.S. Publication No. 2004/0091926 A1). The Office alleges that Liu discusses identifying an siRNA that "uniquely targets CLPP1 that is implicated in cancer cell growth" using the method presently claimed. Applicants respectfully disagrees.

Liu fails to anticipate the presently claimed invention because it is not prior art. As discussed above, the presently claimed invention is entitled to the filing date of the '498 application. The filing date of the '489 application is October 22, 2003. Therefore, the effective filing date of the present application is at least October 22, 2003. The priority date of Liu is October 24, 2003, which is two days after the effective filing date of the present application. Accordingly, Liu is not available as prior art against the present application.

Even if Liu is available as prior art, Liu still fails to anticipate the presently claimed invention because Liu does not explicitly or inherently teach each and every element of the claims. For a reference to anticipate a claim the reference must teach each and every element as it is arranged in the claim. Liu fails to disclose all the elements of claims 1 and 2. For example, Liu fails to disclose or suggest comparing or identifying a uniquely targeting siRNA that includes a step of comparing or identifying at least 11 consecutive nucleotides complementary to the target mRNA sequence including the nucleotide that is third from an siRNA nucleotide sequence's 5' end.

Liu discloses other methods of selecting siRNAs. For example, at paragraph 107, Liu states:

> The siRNA targets can be selected by scanning an mRNA sequence for AA dinucleotides and recording the 19 nucleotides immediately downstream of the AA. Other methods can also been used to select the siRNA targets. In one example, the selection of the siRNA target sequence is purely empirically determined (see e.g., Sui et al., Proc. Natl. Acad. Sci. USA 99: 5515-5520, 2002), as long as the target sequence starts with GG and does not share significant sequence homology with other genes as analyzed by BLAST search. In another example, a more elaborate method is employed to select the siRNA target sequences. This procedure exploits an observation that any accessible site in endogenous mRNA can be targeted for degradation by synthetic oligodeoxyribonucleotide/RNase H method (Lee et al., Nature Biotechnology 20:500-505, 2002).

Although, the resulting siRNA selected by Liu may be equivalent to the siRNA identified by the presently claimed invention, the method to identifying the siRNA is completely different. Liu does not disclose or suggest a step of comparing or identifying at least 11 consecutive

nucleotides complementary to the target mRNA sequence including the nucleotide that is third from an siRNA nucleotide sequence's 5' end. The Office appears to be comparing the resulting product rather than the method used to identify the product. The presently claimed invention is not to the product itself, but rather to the method of identifying the product. The Office has failed to point to anywhere in Liu that discloses all the elements of the presently claimed invention. Therefore, the Liu reference fails to anticipate the presently claimed invention.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Claims 1-6, 13, and 48-51 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Elbashir *et al.* (Methods, 2002, 26:199-213). The Office alleges that Elbashir discloses identifying a uniquely targeting siRNA nucleotide sequence and discloses each and every element of the claim. Applicants respectfully disagree.

Elbashir fails to anticipate the presently claimed invention because Elbashir fails to disclose comparing a database of mRNA sequences from the target species with an siRNA nucleotide sequence that consists of 18-25 nucleotides including at least 11 consecutive nucleotides complementary to the target mRNA sequence to be cleaved by the siRNA nucleotide sequence, wherein the at least 11 consecutive nucleotides complementary to the target mRNA sequence include a nucleotide that is third from an siRNA nucleotide sequence's 5' end (claim 1); or identifying an siRNA nucleotide sequence for the target mRNA, said sequence consisting of 18-24 nucleotides including a nucleotide sequence that has 11 consecutive nucleotides, including the third nucleotide from the siRNA nucleotide sequence's 5' end, that are complementary to an 11 nucleotide sequence that occurs on the target mRNA molecule (claim 2).

The Office also appears to be mischaracterizing the presently claimed invention. the Office only refers to 11 consecutive nucleotides from the 5' end of the sequence. However, the Office fails to take into account that the claims also states that the 11 consecutive nucleotides must also include the 3rd nucleotide from 5' end of the sequence. Elbashir fails to teach or suggest a method of identifying a siRNA sequence that includes a step of comparing or

identifying at least 11 consecutive nucleotides complementary to the target mRNA sequence including the nucleotide that is third from an siRNA nucleotide sequence's 5' end. Elbashir only refers to consecutive nucleotides but never makes reference to the third nucleotide from the sequences 5' end. Therefore, Elbashir fails to teach each and every element of the claim.

Accordingly, Elbashir fails to anticipate the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

***Claim Rejections Under 35 U.S.C. § 103***

Claims 1-6, 10, 13, and 48-52 stand rejected under 35 U.S.C. § 103(a) allegedly being unpatentable over Elbashir *et al* in view of Tuschl *et al.*(WO 03/099298), Martinez *et al.* (*Cell*, 2002, 110:563-574) and Ureta-Vidal *et al.* (*Nature Reviews Genetics*, 2003, 4:251-262). Applicants respectfully disagree.

The combination of references fail to render the presently claimed invention unpatentable because the combination does not yield the presently claimed invention. As discussed above Elbashir fails to teach or suggest comparing a database of mRNA sequences from the target species with an siRNA nucleotide sequence that consists of 18-25 nucleotides including at least 11 consecutive nucleotides complementary to the target mRNA sequence to be cleaved by the siRNA nucleotide sequence, wherein the at least 11 consecutive nucleotides complementary to the target mRNA sequence include a nucleotide that is third from an siRNA nucleotide sequence's 5' end (claim 1); or identifying an siRNA nucleotide sequence for the target mRNA, said sequence consisting of 18-24 nucleotides including a nucleotide sequence that has 11 consecutive nucleotides, including the third nucleotide from the siRNA nucleotide sequence's 5' end, that are complementary to an 11 nucleotide sequence that occurs on the target mRNA molecule (claim 2). The remaining references fail to cure this deficiency. None of the references discuss or suggest the importance of the third nucleotide from the 5' end of the siRNA nucleotide sequence. Accordingly, even if the references are combined the combination does not yield the presently claimed invention.

The Office appears to be misconstruing the method of identifying a uniquely targeting siRNA molecule. The Office appears to be interpreting the method as comparing or identifying 11 consecutive nucleotides that are from the 5' end of the siRNA nucleotide sequence. However, the Office's interpretation of the claims is not correct. The presently claimed invention requires either a step of comparing or identifying at least 11 consecutive nucleotides complementary to the target mRNA sequence including the nucleotide that is third from an siRNA nucleotide sequence's 5' end. There is nothing in the references, alone or in combination, that discusses either of these steps.

Accordingly, the presently claimed invention is not obvious because the combination fails to yield the presently claimed invention. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

**Conclusion**

Claims 1-5, 10, 13, 39 and 48-50, and 52 are in condition for allowance. A notice of allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully Submitted,

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